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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/319,521	06/04/1999	MARK F. PITTENGER	640100-326	3211

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/319,521	**Applicant(s)** PITTENGER ET AL.	
	Examiner Michail A. Belyavskyi	**Art Unit** 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 December 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *27 December 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: _____.

   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

1. Claims 60-79 stand rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,908,784 as evidenced by Cellgro catalog and US Biological Cataloge (2004) and Williams et al., for the same reasons set forth in the previous Office Action, mailed on 06/29/05

Applicant's arguments, filed 12/27/05 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) although US Patent'784 disclosed the use of DMEM as the example of the medium which may be used to promote chondrogenesis it does not includes sugar in an amount of from about 3g/l to about 7 g/l.. The examiner relies on additional reference in order to formulate the rejection, (ii) US Biological Cataloge and Williams et al., are not prior art, because they were published after the filing date of Applicant's provisional application.

With regards to Applicant's comments that US Biological Cataloge and Williams et al., are not prior art. It is noted that said references were used as evidential references not as a prior art references. It is well settled that references which do not qualify as prior art because they post date the claim invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made Ex parte Erlich, 22USPQ 1463 (Bd.Pat.APP&Inter.1992); MPEP 2124.

In the instant case as evidence by Cellgro Catalog and US Biological Cataloge one skill in the art at the time the invention was made would know that the glucose content in DMEM, IMEM, Mc Coy5A is about 4.5 g/l. Said concentration is a species of genus glucose concentration from about 3 g/l to about 7 g/l as claimed in claims 60-79. Moreover, as is evidenced by Williams et al., one skilled in the art at the time the invention was made would know that a chondrogenic medium consists of high –glucose Dulbecco's modified Eagle's medium (DMEM) (see entire documenr, page 681 in particular).
The US Patent 784 teaches a process for producing chondrocytes from mesenchymal stem cells and a process for inducing chondrogenesis in mesenchymal stem cells comprising culturing human mesenchymal stem cells in vitro in a three dimensional format with at least one chondroinductive agent. US Patent '784 teaches that any serum-free animal medium can be used, including DMEM, IMEM, Mc Coy5A and BGJb medium (see column 4, lines 25-35 in particlular). One skilled in the art would immediately recognized said medium as medium with high glucose content not as medium with low glucose content, as is evidenced by Cellgro catalog and US Biological Cataloge (2004) and Williams et al. The mesenchymal stem cells are preferably isolated, culture expanded human mesenchymal stem cells in a chemically defined serum free environment and are condensed in close proximity, such as in the form of a three - dimensional cell mass, e.g. packed cells or a centrifugal pellet or in a ceramic cube. The chondroinductive agent is preferably selected, individually or in combination from the group consisting of: 1) a glucocorticoid such as dexamethasone; ii) a member of the transforming growth factor beta super family (TGF –b) such as BMP-2 or BMP-4, TGF-b1; iii) a component of the collagenous extracellular matrix such as collagen 1; and IV) a vitamin A analog such as retinoic acid. Particularly preferred is the combination of dexamethasone and TGF-beta-1, (see entire patent, especially column 2, lines 5-33, and column 9, lines 45-50).

A species will anticipate a claim to a genus. See MPEP 2131.02.

2. Claims 80- 99 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,908,784 as evidenced by Cellgro catalog and newly cited US Biological Cataloge (2004) and Williams et al., in view of US Patent 5,368,858 for the same reasons set forth in the previous Office Action, mailed on 06/29/05

Applicant's arguments, filed 12/27/05 have been fully considered, but have not been found convincing.

Applicant asserts that since Johnstone et al., US Biological Cataloge and Williams et al., are not the prior art references they can be used in combination with any other references.

Contrary to Applicant's assertion it is noted that: (i) the instant claims are rejected over US Patent 5,908,784, not over Johnstone et al. (ii) US Biological Cataloge; Cellgro catalog and Williams et al., were used as an evidential references not as a prior art references.

The teaching of US Patent 5,908,784, has been discussed, supra.

The US Patent '784, does not explicitly teach the use of TGF-b3.

US Patent '858 teaches the use of TGF-b3 in a method of proliferating chondrocytes and states that the activity among members of the TGF-b family are similar (see entire patent including colllmn 8, 1ines7-24). US Patent '784 also teaches that mesenchymal cells when exposed to TGF-b3 will be transformed into a chondrocytes (see entire patent, including column 5, lines 28-33 and 59-67, and claim 1). US Patent '858 also teaches that dosages of 2-10 ng/ml of TGF-b3 (see entire patent, column 18 and claim 1 in particular)

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent ' 858 to those of US Patent 784 to obtain a claimed process for producing chondrocytes from mesenchymal stem cells using TGF-b3 as one of the chondrioinductive agent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because the activity among members of the TGF-b family are similar, that TGF-b3 can be used in a method of proliferating chondrocytes, and that

mesenchymal cells when exposed to TGF-b3 will be transformed into a chondrocytes as taught by US Patent 858. Thus one member of TGF-b family, i.e. TGF-b1 can be substituted for other member of TGF-b family, i.e TGF-b3 in a process for producing chondrocytes from mesenchymal stem cells taught by US Patent '784. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.
From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

3. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 20, 2006

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